UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

S.M.

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,525	02/05/2002	Karla Robotti	10011206	2898

22878 7590 02/24/2004

AGILENT TECHNOLOGIES, INC.
INTELLECTUAL PROPERTY ADMINISTRATION, LEGAL DEPT.
P.O. BOX 7599
M/S DL429
LOVELAND, CO 80537-0599

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S/14.

Office Action Summary	Application No.	Applicant(s)	
	10/072,525	ROBOTTI, KARLA	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-56,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/5/02*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Claims 1-59 are pending in the present application.

Applicant's election without traverse of Group I (claims 1-56 and 58-59; with the biological material being a polynucleotide, a gene or a gene fragment) in the Response to Restriction requirement dated 11/17/03 is acknowledged.

However, upon further consideration Examiner would like to rejoin the inventions of Groups I-III for the present examination, with the biological material being a polynucleotide, a gene or a gene fragment, or an enzyme or an antibody or a coagulation modulator, or a cell membrane or a membrane fragment.

Claim 57 is withdrawn from further consideration because it is drawn to non-elected invention.

Claims 1-56 and 58-59 are examined on the merits herein.

Claim Objections

Claim 59 is objected to because it contains the non-elected embodiment, specifically the non-elected claim 57. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 46-55 recite the limitation "the bed" in line 2 of claim 46, and line 1 of claims 47 and 48. There is insufficient antecedent basis for this limitation in the claim. Please note that in claim 45, there is no recitation of any bed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 9-11, 16-17, 24-43 are rejected under 35 U.S.C. 102(e) as being anticipated by Liu et al. (US 6,303,290; IDS).

Liu et al. teach an alcohol-free method of making a porous, inorganic matrix containing a biological material encapsulated therein, comprising: (a) forming an aqueous composition comprising a ceramic oxide colloidal sol mixed with an acidified oxide salt solution, which is transformed into a polymerizing hydroxide solution, and wherein the resulting composition has a pH ranging from 6.2 to 8.2; (b) adding to said

composition an amount of the biological material in a physiologically acceptable-buffered solution to form a nanocomposite, wherein the ionic strength of the resulting nanocomposite is adjusted to a physiologically acceptable level by the addition of salts; (c) gently shaking the resulting nanocomposite until it becomes viscous; (d) shaping the viscous, aqueous mixture produced in step (c) into a final form and aging into an aqueous gel; and (e) drying the aged gel slowly in air at a temperature of 4^0C., thereby permitting a portion of the water in the gel to evaporate, wherein the drying gel has a decreased volume as compared with the aged gel of step (d), and molecules of the biological material are encapsulated within pores of the drying or dried gel (col. 3, lines 47-67). The biological material includes RNA, DNA, active proteins, active fragments of DNA, RNA, proteins, enzymes such as RNase, DNase, nuclease, kinase, transferase, trypsin, chymotrypsin, cytochrome c (MW of 12,327) as well as their active fragments and others (col. 4, lines 8-28). The nanocomposite is comprised of colloidal silica sol and dissolved sodium silicate (col. 4, lines 1-3), and is predominantly of a size less than 100 nm (col. 9, lines 32-37), with preferred size ranges from 2 to 50 nm, more preferably of the order of 15-30 nm for encapsulating DNA (col. 13, line 62 continues to line 6 of col. 14). Liu et al. further teach that the aqueous gel is shaped, preferably into a monolithic gel, thin film or fiber (co. 4, lines 35-37), and that the pH of the solutions is adjusted using HCl and/or NH4OH with the preferred pH ranges from about 5 to about 9, preferably from 6 to 8, and more preferably at about pH 6.2-7.2, and including at a constant pH 7.2 (col. 15, lines 5-11 and example 2 at col. 22). Additionally, Liu et al. teach that the gel is aged and dried over a period of 2-4 weeks (col. 20, lines 23-25).

Liu et al. further disclose a method for the quantitative or qualitative detection of a test substance that reacts with or whose reaction is catalyzed by an active biological material, wherein the biological material is encapsulated within the aforementioned nanocomposite. The quantitative/qualitative method comprises the step of bringing the biological-material containing nanocomposite into contact with a gas or aqueous solution comprising the test substance, and qualitatively or quantitatively detecting, observing or measuring the change in one or more optical characteristics in the biological material encapsulated within the nanocomposite. The change in one or more optical characteristics of the encapsulated biological material is qualitatively or quantitatively measured by spectroscopy utilizing one or more techniques such as UV, IR, visible light, fluorescence, luminescence, absorption, emission, excitation and reflection (col. 4, line 62 continues to line17 of col. 5). Since the aqueous hydogen peroxide (H_2O_2) is in contact and is catalyzed by the catalase-doped silica gel of Liu et al. (see example 5), molecules having a mass of 3,000 Da or less can diffuse through the pores of the gel.

Accordingly, Liu et al. anticipate the instant claims.

Claims 1-6, 9-10, 12, 15-16, 18, 21, 24-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunn et al. (U.S. Patent No. 5,200,334; IDS).

Dunn et al. teach a process for the production of a porous, transparent sol-gel glass containing an alcohol sensitive active biological material entrapped therein comprising: (a) forming a single phase sol by mixing a metal alkoxide in a non-alcoholic

medium comprising water and an acid catalyst in a container exposed to ultrasonic energy, the mixture having a pH not greater than about 2; (b) removing the ultrasonic energy and raising the pH of the sol to about 5 to 7 by the addition of a buffering agent; 9c) adding an alcohol sensitive active biological material to the buffered sol; (d) forming a gel and allowing the gel to age; and (e) allowing at least a portion of the water in the gel to evaporate so that the volume of the product produced in step (d) is decreased and the active biological material is trapped in a monolith of the gel having a reduced volume (see abstract, Fig. 1 and claim 1). Although exemplified method utilizes tetramethylorthosilicate (TMOS), and proteins (e.g., RNase A, proteases, hemoglobin, cytochrome c, metal ion binders, see col. 3, lines 38-59 and Table 1) as active biological materials, however other silicon alkoxides such as tetraethylorthosilicate (TEOS) and other active silicon compounds as well as other metal alkoxides (not limited to aluminium, titanium, zirconium, vanadium, sodium, calcium and boron or combinations thereof) can be used (col. 2, line 60 continues to line 10 of col. 3). In an exemplified method, the gel is allowed to age at room temperature for 7 to 21 days (col. 5, lines 2-8, 17-19). The porous, transparent sol-gel glass has a median pore radius of about 15 Angstroms (1.5 nm) and a maximum pore radius of about 100 Angstroms or 10 nm (see Fig. 2, claim 22). Dunn et al. further teach that the process results in a product useful for forming into sensors for qualitatively and quantitatively detecting the presence of numerous compounds, both organic and inorganic, which react with the entrapped material. Additionally, because of the optical transparency of the glass, photometric detection techniques can be utilized to monitor the changes in the entrapped enzyme or

its environment resulting from its use (col. 2, lines 6-13). Dunn et al. further teach that it would be highly advantageous to encapsulate enzymes in a porous, transparent glass structure, such as structures prepared by the sol-gel process. Such an encapsulation would be significantly easier to minaturize and would be far less cumbersome and far more reliable than membrane encapsulating systems. Furthermore, enzyme encapsulation within a transparent glass structure would allow for the monitoring of many enzymatic reactions by using simple, photometric monitoring systems (col. 1, lines 27-36). Since glucose and o-dianisidine substrates are in contact and they are catalyzed by glucose oxidase and peroxidase-doped silica gel of Dunn et al. (see example 3), molecules having a mass of 3,000 Da or less can diffuse through the pores of the gel.

Accordingly, Dunn et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 7-8, 9, 12, 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn et al. (U.S. Patent No. 5,200,334; IDS) or Liu et al. (US 6,303,290; IDS) in view of Avnir et al. (U.S. Patent No. 5,300,564; IDS).

Dunn et al. teach a process for the production of a porous, transparent sol-gel glass containing an alcohol sensitive active biological material entrapped therein comprising: (a) forming a single phase sol by mixing a metal alkoxide in a non-alcoholic medium comprising water and an acid catalyst in a container exposed to ultrasonic energy, the mixture having a pH not greater than about 2; (b) removing the ultrasonic energy and raising the pH of the sol to about 5 to 7 by the addition of a buffering agent; 9c) adding an alcohol sensitive active biological material to the buffered sol; (d) forming a gel and allowing the gel to age; and (e) allowing at least a portion of the water in the gel to evaporate so that the volume of the product produced in step (d) is decreased and the active biological material is trapped in a monolith of the gel having a reduced volume (see abstract, Fig. 1 and claim 1). Although exemplified method utilizes tetramethylorthosilicate (TMOS), and proteins (e.g., RNase A, proteases, hemoglobin, cytochrome c, metal ion binders, see col. 3, lines 38-59 and Table 1) as active biological materials, however other silicon alkoxides such as tetraethylorthosilicate (TEOS) and other active silicon compounds as well as other metal alkoxides (not limited to aluminium, titanium, zirconium, vanadium, sodium, calcium and boron or **combinations thereof**) can be used (col. 2, line 60 continues to line 10 of col. 3). Dunn et al. further teach that **it would be highly advantageous to encapsulate enzymes in a porous, transparent glass structure, such as structures prepared by the sol-gel process. Such an encapsulation would be significantly easier to minaturize and would be far less cumbersome and far more reliable than membrane encapsulating systems**. Furthermore, enzyme encapsulation within a transparent glass structure

would allow for the monitoring of many enzymatic reactions by using simple, photometric monitoring systems (col. 1, lines 27-36).

Liu et al. teach an alcohol-free method of making a porous, inorganic matrix containing a biological material encapsulated therein, comprising: (a) forming an aqueous composition comprising a ceramic oxide colloidal sol mixed with an acidified oxide salt solution, which is transformed into a polymerizing hydroxide solution, and wherein the resulting composition has a pH ranging from 6.2 to 8.2; (b) adding to said composition an amount of the biological material in a physiologically acceptable-buffered solution to form a nanocomposite, wherein the ionic strength of the resulting nanocomposite is adjusted to a physiologically acceptable level by the addition of salts; (c) gently shaking the resulting nanocomposite until it becomes viscous; (d) shaping the viscous, aqueous mixture produced in step (c) into a final form and aging into an aqueous gel; and (e) drying the aged gel slowly in air at a temperature of 4^0C., thereby permitting a portion of the water in the gel to evaporate, wherein the drying gel has a decreased volume as compared with the aged gel of step (d), and molecules of the biological material are encapsulated within pores of the drying or dried gel (col. 3, lines 47-67). The biological material includes RNA, DNA, active proteins, active fragments of DNA, RNA, proteins, enzymes such as RNase, DNase, nuclease, kinase, transferase, trypsin, chymotrypsin, cytochrome c (MW of 12,327) as well as their active fragments and others (col. 4, lines 8-28). The nanocomposite is comprised of colloidal silica sol and dissolved sodium silicate (col. 4, lines 1-3), and is predominantly of a size less than 100 nm (col. 9, lines 32-37), with preferred size ranges from 2 to 50 nm, more

preferably of the order of 15-30 nm for encapsulating DNA (col. 13, line 62 continues to line 6 of col. 14). Liu et al. further disclose a method for the quantitative or qualitative detection of a test substance that reacts with or whose reaction is catalyzed by an active biological material, wherein the biological material is encapsulated within the aforementioned nanocomposite. The quantitative/qualitative method comprises the step of bringing the biological-material containing nanocomposite into contact with a gas or aqueous solution comprising the test substance, and qualitatively or quantitatively detecting, observing or measuring the change in one or more optical characteristics in the biological material encapsulated within the nanocomposite.

Neither Dunn et al. nor Liu et al. teach explicitly that the aged gel is crushed into particulates, preferably those between about 10 μm to about 80 μm in diameter.

However, at the filing date of the present application, Avnir et al. already teach obtaining a chemical interaction between at least one reagent trapped in sol-gel glass by doping it with the reagent, and diffusible solutes or components in an adjacent liquid or gas phase. The reagents, the solutes and the components can be any organic or inorganic compounds or materials of biological origin including enzymes (see abstract). Avnir et al. further teach that the doped sol-gel glass can be in any shape suitable for the test, for example, it can have the shape of rods, discs, cubes, sieves, powder or thin films coating conventional glass plates or any other inert solid support (col. 3, lines 20-24). Avnir et al. also teach that the doped sol gel glasses can be used for all chromatographic purposes including liquid, gas and thin layer chromatography. The extraction or separation is performed by passing the solution through columns made

from appropriately doped sol gel material (col. 3, lines 445-52). Particularly, Avnir et al. teach that for sol-gel immobilized enzymes, **crushed powder sol gel glasses may be used as support for enzymatic column chromatography**, with an exemplification showing that the glasses were ground to a size about 60-100 mesh (col. 5, lines 37-39, and col. 7, lines 55-57).

Accordingly, at the effective filing date of the present application, it would have been obvious for an ordinary skilled artisan in the art to modify the method taught by Dunn et al. or Liu et al. by further crushing their aged sol gel glasses into particulates, including those between about 10 μm to about 80 μm in diameter in light of the teachings of Avnir et al. for use as support for enzymatic column chromatography.

An ordinary skilled artisan would have been motivated to carry out the above modification because Avnir et al. already teach that crushed powder sol gel glasses may be used as support for enzymatic column chromatography, and that the doped sol gel glasses can be used for all chromatographic purposes including liquid, gas and thin layer chromatography. Additionally, the sol-gel glasses prepared by either method of Dunn et al. or Liu et al. retain a high level of activity, particularly for an alcohol sensitive active biological material entrapped in a porous, transparent sol-gel glass.

An ordinary skilled artisan would have a reasonable expectation of success based on the teachings of Dunn et al. or Liu et al. and Avnir et al., as well a high level of skill of an ordinary skilled artisan in the art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 9, 12-14 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn et al. (U.S. Patent No. 5,200,334) in view of Reetz et al. (Biotechnology and Bioengineering, Vol. 9:527-534, 1996).

The teachings of Dunn et al. have already been presented above. However, Dunn et al. do not specifically teach a method wherein the sol comprises a tetralkyl orthosilicate and a silane substituted with at least two leaving groups selected from the group consisting of OR and halo, or wherein the silane is substituted with a C_8-C_{24} alkyl group or wherein the alkyl group is C_{18}.

However, at the filing date of the present application Reetz et al. teach that lipase activity in gels from a mixture of tetramethoxysilane (TMOS) and alkyltrimethoxysilanes $Rsi(OCH_3)_3$ was dramatically enhanced with increasing amount and alkyl chain length of the hydrophobic silanes, including the alkyl group C_{18} (page 529, right-handed column, first complete paragraph and Figure 1).

Accordingly, at the effective filing date of the present application, it would have been obvious for an ordinary skilled artisan in the art to modify the method taught by Dunn et al. by further introducing a substituted silane as recited in the sol in light of the teachings of Reetz et al. due to the stabilizing effect on entrapped lipase by increasing amount and alkyl chain length of the hydrophobic silanes.

An ordinary skilled artisan would have been motivated to carry out the above modification because increasing amount and alkyl chain length of the hydrophobic

silanes, including the alkyl group C_{18} enhance lipase-doped sol-gel as taught by Reetz et al.

An ordinary skilled artisan would have a reasonable expectation of success based on the teachings of Dunn et al. and Reetz et al., as well a high level of skill of an ordinary skilled artisan in the art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 44-56 and 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn et al. (U.S. Patent No. 5,200,334; IDS) in view of Avnir et al. (U.S. Patent No. 5,300,564; IDS), Swedberg et al. (U.S. Patent No. 6,240,790) and Freeman et al. (U.S. Patent No. 6,194,900).

Dunn et al. teach a process for the production of a porous, transparent sol-gel glass containing an alcohol sensitive active biological material entrapped therein, including in the form of thin films as small as 1000 Angstroms thick or shaped gels having dimensions in its smallest direction of at least 0.5 cm or a monolith (see Summary and col. 2, lines 1-5). Exemplified method utilizes tetramethylorthosilicate (TMOS), and proteins (e.g., RNase A, proteases, hemoglobin, cytochrome c, metal ion binders, see col. 3, lines 38-59 and Table 1) as active biological materials. Dunn et al. further teach that **encapsulated or entrapped enzymes are used with increasing frequency as micro-catalysts and analytical devices of very high sensitivity, and that enzymes have been enclosed in membranes systems and used as high-**

<u>sensitivity monitoring devices. However, such membrane systems are cumbersome and difficult to miniaturize. Therefore, it would be highly advantageous to encapsulate enzymes in a porous, transparent glass structure, such as structures prepared by the sol-gel process. Such an encapsulation would be significantly easier to miniaturize and would be far less cumbersome and far more reliable than membrane encapsulating systems</u> (col. 1, lines 27036). Additionally, enzyme encapsulation within a transparent glass structure would allow for the monitoring of many enzymatic reactions by using simple, photometric monitoring systems (col. 1, lines 27-36). Because of the light transmission characteristics of the glases, UV, IR and visible light optical spectroscopy as well as fluorescence, luminescence, absorption, emission and reflection techniques are all suitable for quantitative and/or qualitative monitoring of chemical changes produced by the sol-gel glasses with entrapped enzymes (col. 4, lines 49-56).

<u>Dunn et al. does not teach explicitly a method of preparing any microanalytical device containing a sol-gel comprising an entrapped biological molecule, or a method of using the miroanalytical device</u>.

However, at the filing date of the present application, Avnir et al. already teach obtaining a chemical interaction between at least one reagent trapped in sol-gel glass by doping it with the reagent, and diffusible solutes or components in an adjacent liquid or gas phase. The reagents, the solutes and the components can be any organic or inorganic compounds or materials of biological origin including enzymes (see abstract). Avnir et al. further teach that the doped sol-gel glass can be in any shape suitable for

the test, for example, it can have the shape of rods, discs, cubes, sieves, powder or thin films coating conventional glass plates or any other inert solid support (col. 3, lines 20-24). Avnir et al. also teach that the doped sol gel glasses can be used for all chromatographic purposes including liquid, gas and thin layer chromatography. The extraction or separation is performed by passing the solution through columns made from appropriately doped sol gel material (col. 3, lines 445-52). Particularly, Avnir et al. teach that for sol-gel immobilized enzymes, **crushed powder sol gel glasses may be used as support for enzymatic column chromatography**, with an exemplification showing that the glasses were ground to a size about 60-100 mesh (col.
5, lines 37-39, and col. 7, lines 55-57).

Swedberg et al. already teach a high-throughput microanalysis device having a plurality of sample processing compartments for use in analysis of small and/or macromolecular and/or other solutes in the liquid phase (see abstract). The device is formed by microfabrication of microstructures. Swedberg et al. also teach that the microanalysis device is interfaced with any analytical detection means well known in the art, such as UV/Vis, Near IR, fluorescence, refractive index (RI), Raman techniques, as well as Mass spectrometry (MS) and NMR (col. 6, lines 3-11).

Freeman et al. also teach a miniaturized total analysis system with an in-line NMR detection compartment for the analysis of small and/or macromolecular and/or other solutes in the liquid phase (see abstract).

Accordingly, at the effective filing date of the present application, it would have been obvious for an ordinary skilled artisan in the art to modify the teachings for Dunn et

al. by forming a micro-analytical device containing their biological material doped sol-gel and using such micro-analytical device for analysis of small and/or macromolecular and/or other solutes in the liquid phase in light of the teachings of Avnir et al, Swedberg et al., and Freeman et al. because the encapsulated biological material (e.g., enzymes) prepared by the sol-gel process is easier to miniaturize and less cumbersome for use in analytical devices of very high sensitivity such as those taught by Swedberg et al. and Freeman et al. for achieving high throughput sample processing and analysis as well as fast time-to-result analysis of biological liquids in a truly integrated fashion.

An ordinary skilled artisan would have been motivated to carry out the above modification because Dunn et al. already teach that encapsulated biological material (e.g., enzymes) prepared by the sol-gel process is easier to miniaturize and less cumbersome for use in analytical devices of very high sensitivity, Avnir et al. dislose that doped sol gel glasses (including enzyme-doped sol gel glasses are crushed to be used as support for enzymatic column chromatography) for all chromatographic purposes including liquid, gas and thin layer chromatography, and that the micro-devices taught by Swedberg et al. and Freeman et al. that are used for analysis of small and/or macromolecular solutes in the liquid phase allow high throughput sample processing and analysis as well as fast time-to-result analysis of biological liquids in a truly integrated fashion.

An ordinary skilled artisan would have a reasonable expectation of success based on the teachings of Dunn et al., Avnir et al., Swedberg et al. (U.S. Patent No.

5,571,410) and Freeman et al., as well a high level of skill of an ordinary skilled artisan in the art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636, Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

JAMES KETTER
PRIMARY EXAMINER